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1: J Immunol Methods. 1995 Jan 27;178(2):173-81.

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Characterization of the apoptotic effects of human tumor necrosis factor: development of highly rapid and specific bioassay for human tumor necrosis factor and lymphotoxin using human target cells.

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Higuchi M, Singh S, Aggarwal BB.

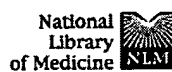
Department of Clinical Immunology and Biological Therapy, University of Texas M. D. Anderson Cancer Center, Houston 77030.

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Currently available bioassays for most cytokines require several days and therefore must be performed under sterile conditions. In this report we describe a bioassay for tumor necrosis factor (TNF) and lymphotoxin (LT) that is extremely rapid and specific and does not require sterile conditions. Using tritiated thymidine release, we could conveniently monitor degradation of DNA into small fragments following the incubation of human myelogenous leukemia ML-1a cells with TNF. The assay showed that TNF-dependent DNA fragmentation was potentiated by cycloheximide and occurred within 90 min. Treatment of cells to TNF lead to apoptosis as indicated by thymidine release, DNA laddering on agarose gels and morphological alterations. Under these conditions, plasma membrane were not damaged as indicated by lack of chromium release. This effect was linear with TNF concentration. This assay had high throughput, did not require sterile conditions, could be carried out in the absence of serum, and was sensitive only to TNF and LT and not to interferon (IFN)-alpha, IFN-beta, IFN-gamma, transforming growth factor beta, interleukin-4, leukemia inhibitory factor and granulocyte-monocyte colony stimulating factor; all cytokines known to inhibit different cell types. Besides detection of TNF in biological fluids, this assay may prove useful for the identification of novel inhibitors of TNF action.

PMID: 7836779 [PubMed - indexed for MEDLINE]

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Tumor cell resistance to apoptosis due to a defect in the activation of sphingomyelinase and the 24 kDa apoptotic protease (AP24).

Wright SC, Zheng H, Zhong J.

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Palo Alto Institute of Molecular Medicine, Mountain View, California 94043, USA.

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Signal transduction pathways involved in apoptotic cell death are poorly understood, although recent studies have implicated sphingomyelin hydrolysis and generation of the second messenger, ceramide. Previous work in this laboratory demonstrated that a serine protease termed AP24 was activated by TNF or UV light and induced DNA fragmentation in isolated nuclei. This study extended these findings to examine the role of these enzymes in apoptosis of the U937 cell line and the mechanism of resistance of its variant, U9-TR. Although this subclone was selected by growth in TNF, it was unexpectedly found to resist apoptosis induced by UV light, but was still sensitive to anti-Fas-induced DNA fragmentation. Here we show that in contrast to normal U937 cells, UV light and TNF both failed to activate neutral or acidic sphingomyelinase or AP24 in the U9-TR variant. However, anti-Fas activated both neutral and acidic sphingomyelinase in the variant comparable to that seen in parental U937. The U9-TR variant could be sensitized to TNF or UV light activation of both sphingomyelinase and DNA fragmentation by the protein phosphatase inhibitors okadaic acid and calyculin A. Furthermore, exogenous bacterial-derived sphingomyelinase caused U9-TR activation of AP24 and DNA fragmentation comparable to that in the parental U937. Exposure of permeabilized U937 cells to ceramide caused internucleosomal DNA cleavage that was blocked by an inhibitor of AP24. Taken altogether, these findings demonstrate that TNF or UV light activate sphingomyelinase that leads to the generation of ceramide resulting in activation of AP24 and DNA fragmentation in sensitive cells. A selective defect in signals leading to sphingomyelinase activation can confer resistance to apoptosis even though the variant is still sensitive to downstream apoptotic signals such as nuclear DNA fragmentation by activated exogenous AP24.

PMID: 8641566 [PubMed - indexed for MEDLINE]

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1: J Exp Med. 1994 Aug 1;180(2):525-35.

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Ionizing radiation acts on cellular membranes to generate ceramide and initiate apoptosis.

Haimovitz-Friedman A, Kan CC, Ehleiter D, Persaud RS, McLoughlin M, Fuks Z, Kolesnick RN.

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Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10021.

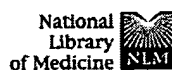
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Recent investigations provided evidence that the sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor alpha (TNF-alpha) in several hematopoietic and nonhematopoietic cells. In this pathway, TNF-receptor interaction initiates sphingomyelin hydrolysis to ceramide by a sphingomyelinase. Ceramide acts as a second messenger stimulating a ceramide-activated serine/threonine protein kinase. The present studies show that ionizing radiation, like TNF, induces rapid sphingomyelin hydrolysis to ceramide and apoptosis in bovine aortic endothelial cells. Elevation of ceramide with exogenous ceramide analogues was sufficient for induction of apoptosis. Protein kinase C activation blocked both radiation-induced sphingomyelin hydrolysis and apoptosis, and apoptosis was restored by ceramide analogues added exogenously. Ionizing radiation acted directly on membrane preparations devoid of nuclei, stimulating sphingomyelin hydrolysis enzymatically through a neutral sphingomyelinase. These studies provide the first conclusive evidence that apoptotic signaling can be generated by interaction of ionizing radiation with cellular membranes and suggest an alternative to the hypothesis that direct DNA damage mediates radiation-induced cell kill.

PMID: 8046331 [PubMed - indexed for MEDLINE]

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Inhibition of lysosomal acid sphingomyelinase by agents which reverse multidrug resistance.

Jaffrezou JP, Chen G, Duran GE, Muller C, Bordier C, Laurent G, Sikic BI, Levade T.

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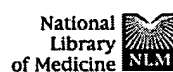
Department of Medicine, Stanford University Medical Center, CA 94305, USA.

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An increasing body of evidence appears to implicate the lipid bilayer of multidrug resistant (MDR) cells with P-glycoprotein activity. Several cationic amphiphilic drugs (CADs) have been extensively described as modulators of MDR. These same agents are also known to (1) inhibit lysosomal acid sphingomyelinase (ASmase), a phospholipid degrading enzyme, and/or (2) induce phospholipidosis in animal tissues or cultured cell lines. In this report, we randomly selected 17 CADs and evaluated their potency in modulating MDR in the murine MDR P388/ADR leukemia cell line. We compared these results with their ability to inhibit ASmase and observed a significant dose-dependent linear relationship (95% central confidence interval), between ASmase inhibition and MDR reversal. This approach permitted us to identify three new modestly potent chemosensitizers: trimipramine, desipramine, and mianserine. Modulation of MDR was not cell line specific, since CADs at 10 microM increased doxorubicin (DOX) and vinblastine (VBL) (but not methotrexate, MTX) cytotoxicity in both P388/ADR and the human MDR cell lines MES-SA/Dx5 and K562/R7, but not in the parental drug-sensitive cells. Although all chemosensitizing CADs at 10 microM significantly increased Rhodamine-123 (Rho-123) accumulation in the human leukemia MDR cell line K562/R7 and most presented significant displacement of the photoaffinity labelling probe iodoarylazidoprazosin, no correlation between these observations and the ability of CADs to sensitize MDR cells to DOX and VBL was found. In conclusion, our study strongly suggests that the chemosensitizing potency of agents such as CADs may be due to a dual mechanism of action: direct antagonism of P-gp activity and indirect modulation of P-gp activity through the disruption of cellular lipid metabolism.

PMID: 7718613 [PubMed - indexed for MEDLINE]

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Distinct p53-independent apoptotic cell death signalling pathways in testicular germ cell tumour cell lines.

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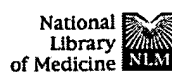
Burger H, Nooter K, Boersma AW, van Wingerden KE, Looijenga LH, Jochemsen AG, Stoter G.

Department of Medical Oncology, University Hospital Rotterdam, Josephine Nefkens Institute, The Netherlands.

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The induction of apoptosis by diverse apoptotic stimuli was studied in a panel of 6 testicular germ cell tumour (TGCT) cell lines with defined p53 status. Although the sensitivity to a particular stimulus varied considerably among the TGCT cell lines, the differences in response were not associated with the presence of functional p53. Mutant (mt) p53-expressing NCCIT and S2 (no p53 protein) were both readily triggered into apoptosis by cisplatin and doxorubicin, while wild-type(wt)-p53-transactivation-competent 2102 EP cells failed to undergo drug-induced apoptosis. Moreover, transactivation-deficient NCCIT cells and wtp53-expressing NT2 cells were equally sensitive to cisplatin, doxorubicin, gamma radiation, and cell-permeable C2-ceramide. Our p53 data suggest that, at least in this panel of non-isogenic TGCT cell lines, hypersensitivity to therapeutic agents is not associated with p53 status. Next, we examined the impact of p53 inactivation on apoptosis induction in isogenic NT2 sublines expressing human papillomavirus E6 protein. Evidently, abrogation of p53 function did not affect the hypersensitivity to apoptotic stimuli. We noted that drug-sensitive S2 cells were highly resistant to radiation-induced apoptosis, indicating distinct signalling pathways for chemotherapy and irradiation. The impaired radiation-induced apoptotic pathway in S2 and 2102 EP could not be restored by addition of cell-permeable C2-ceramide, suggesting that the blockade is downstream of ceramide generation. Ligation of Fas/APO-1/CD95 by anti-Fas effectively induced apoptosis in Fas-antigen expressing S2, 2102 EP and 833 KE. The efficient Fas-mediated activation of apoptosis in drug-, radiation-, and ceramide-resistant 2102 EP cells further suggests that diverse apoptosis-inducing factors may use distinct signalling pathways. In summary, we demonstrated the presence of distinct p53-independent apoptotic pathways in TGCT cells.

PMID: 10225454 [PubMed - indexed for MEDLINE]



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Differential sensitivity to the induction of apoptosis by cisplatin in proliferating and quiescent immature rat thymocytes is independent of the levels of drug accumulation and DNA adduct formation.

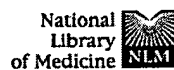
Evans DL, Tilby M, Dive C.

Cancer Research Campaign Cellular and Molecular Pharmacology Group, School of Biological Sciences, Manchester University, United Kingdom.

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Immature rat thymocytes readily undergo apoptosis following exposure to many different stimuli, including agents which cause DNA damage, such as the topoisomerase II inhibitor etoposide and irradiation. We have shown previously that cells isolated from the immature rat thymus are resistant to the induction of apoptosis by the DNA-damaging agent cis-diamminedichloroplatinum(II) (cisplatin) (D. L. Evans and C. Dive, Cancer Res., 53:2133-2139, 1993). More than 85% of these thymocytes are quiescent. Here, we demonstrate that following purification of the minority subpopulation of thymocytes that are proliferating, a 2-h exposure to 50 microM cisplatin resulted in rapid apoptosis with 66% apoptotic cells by 12 h. In contrast, purified, nonproliferating thymocytes treated with cisplatin exhibited control levels of apoptosis at 12 h. Both proliferating and nonproliferating thymocytes rapidly underwent apoptosis following continuous exposure to methylprednisolone (10 microM) and etoposide (10 microM). The discrepancy in the levels of apoptosis seen in proliferating and quiescent thymocytes in response to cisplatin could not be attributed to changes in total cellular levels of cisplatin or to the number of DNA-platinum adducts which were determined, respectively, by atomic absorption spectrometry and competitive enzyme-linked immunoadsorbent assay. These results imply that in contrast to engagement of thymocyte apoptosis by methylprednisolone and etoposide, where apoptosis was proliferation independent, cisplatin-induced apoptosis depends on the presence of cells in S and G2-M phases of the cell cycle. Moreover, comparison of etoposide and cisplatin responses in thymocytes suggests that DNA damage per se may not be sufficient to induce apoptosis and that the type of DNA damage is important in this regard.

PMID: 8137265 [PubMed - indexed for MEDLINE]



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Lipid mediator networks in cell signaling: update and impact of cytokines.

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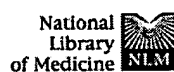
Department of Anesthesia, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.

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Biomembranes serve barrier functions and serve as a store for precursors of rapidly generated, structurally diverse intracellular and extracellular lipid-derived mediators (LM). Cell activation is accompanied by remodeling of membrane components that appear to be essential in signal transduction. Phospholipases (PLA2, PLC, PLD, sphingomyelinase) are pivotal in the generation of these LM including eicosanoids, platelet activating factor (PAF), diacylglycerides, ceramide, and other newly discovered bioactive autacoids. Cytokines exert a dramatic multilevel impact both in regulating enzymes in individual LM pathways and in generating LM central to their action. Here, we provide an overview and update of recent progress in this area with emphasis on the effect of cytokines on LM networks. The generation of eicosanoids (prostaglandins, leukotrienes, and lipoxins), oxygenated lipids, and PAF remain the focus of rational drug design targets given their established roles in cell-cell communication and as mediators in inflammation and pathophysiologic events. Key enzymes in these pathways are cloned, sequenced, and their subcellular organization is investigated with surprising findings implicating involvement of the nuclear membrane at the functional level. Several LM receptors are identified and cloned, and results from transgenic animals have emerged for several key enzymes. Novel bioactive eicosanoids were discovered, including 15-epi-lipoxins, isoprostanes, and isoleukotrienes, that offered new concepts to consider in formation of LM and the actions of nonsteroidal anti-inflammatory drugs. Together, these findings indicate that LM play critical and essential roles in both signal transduction and cell-cell communication and will continue to be important pathways to be considered in novel therapeutic approaches.-Serhan, C. N., Haeggstrom, J. Z., Leslie, C. C. Lipid mediator networks in cell signaling: update and impact of cytokines.

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- Review
- Review, Tutorial



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☐ 1: Curr Opin Oncol 1998 Nov;10(6):552-9

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The role of ceramide in the cellular response to cytotoxic agents.

Jarvis WD, Grant S.

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Department of Medicine, Medical College of Virginia, Richmond 23298-0230, USA.

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The sphingolipid messenger ceramide has been implicated in the initiation of apoptotic cell death in a variety of physiologic settings. Recent investigation has shown that ceramide-dependent stress signaling is associated with chemotherapy-related apoptosis. It is not entirely clear, however, whether drug-mediated generation of ceramide is essential for execution of the cell death program, or simply represents a component of the genotoxic stress response. For example, there is evidence that ceramide subserves an important role in certain stresses (e.g., ionizing radiation, daunorubicin) but represents a secondary process in others (e.g., cytarabine). The review presents evidence for and against a cytotoxic effector function for ceramide in the lethal actions of conventional antineoplastic agents.

Publication Types:

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- Review, Tutorial

PMID: 9818235 [PubMed - indexed for MEDLINE]

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1: Nat Genet. 1995 Jul;10(3):288-93.

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Acid sphingomyelinase deficient mice: a model of types A and B Niemann-Pick disease.

Horinouchi K, Erlich S, Perl DP, Ferlinz K, Bisgaier CL, Sandhoff K, Desnick RJ, Stewart CL, Schuchman EH.

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Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.

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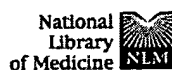
Types A and B Niemann-Pick disease (NPD) result from the deficient activity of acid sphingomyelinase (ASM). An animal model of NPD has been created by gene targeting. In affected animals, the disease followed a severe, neurodegenerative course and death occurred by eight months of age. Analysis of these animals showed their tissues had no detectable ASM activity, the blood cholesterol levels and sphingomyelin in the liver and brain were elevated, and atrophy of the cerebellum and marked deficiency of Purkinje cells was evident. Microscopic analysis revealed 'NPD cells' in reticuloendothelial organs and characteristic NPD lesions in the brain. Thus, the ASM deficient mice should be of great value for studying the pathogenesis and treatment of NPD, and for investigations into the role of ASM in signal transduction and apoptosis.

PMID: 7670466 [PubMed - indexed for MEDLINE]

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1: Cell. 1996 Jul 26;86(2):189-99.

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Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis.

Santana P, Pena LA, Haimovitz-Friedman A, Martin S, Green D, McLoughlin M, Cordon-Cardo C, Schuchman EH, Fuks Z, Kolesnick R.

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Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center New York, New York 10021, USA.


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Stress is believed to activate sphingomyelinase to generate ceramide, which serves as a second messenger in initiating the apoptotic response. Conclusive evidence for this paradigm, however, is lacking. In the present study, we used a genetic approach to address this issue directly. We show that lymphoblasts from Niemann-Pick patients, which have an inherited deficiency of acid sphingomyelinase activity, fail to respond to ionizing radiation with ceramide generation and apoptosis. These abnormalities are reversible up on restoration of acid sphingomyelinase activity by retroviral transfer of human acid sphingomyelinase cDNA. Acid sphingomyelinase knockout mice also expressed defects in radiation-induced ceramide generation and apoptosis in vivo. Comparison with p53 knockout mice revealed that acid sphingomyelinase-mediated apoptosis and p53-mediated apoptosis are likely distinct and independent. These genetic models provide definitive evidence for the involvement of acid sphingomyelinase in one form of stress-induced apoptosis.

PMID: 8706124 [PubMed - indexed for MEDLINE]

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Functions of Ceramide in Coordinating Cellular Responses to Stress

Yusuf A. Hannun

Sphingolipid metabolites participate in key events of signal transduction and cell regulation. In the sphingomyelin cycle, a number of extracellular agents and insults (such as tumor necrosis factor, Fas ligands, and chemotherapeutic agents) cause the activation of sphingomyelinases, which act on membrane sphingomyelin and release ceramide. Multiple experimental approaches suggest an important role for ceramide in regulating such diverse responses as cell cycle arrest, apoptosis, and cell senescence. In vitro, ceramide activates a serine-threonine protein phosphatase, and in cells it regulates protein phosphorylation as well as multiple downstream targets [such as interleukin converting enzyme (ICE)-like proteases, stress-activated protein kinases, and the retinoblastoma gene product] that mediate its distinct cellular effects. This spectrum of inducers of ceramide accumulation and the nature of ceramide-mediated responses suggest that ceramide is a key component of intracellular stress response pathways.

The author is in the Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.

The paradigm of signaling through the glycerophospholipids (1) has taught us a critical lesson in lipid-mediated signal transduction and cell regulation: The structural complexity of membrane glycerophospholipids belies the role they subserve in signal transduction. Second messengers derived from precursor glycerophospholipids include diacylglycerol (DAG), inositol trisphosphate (IP₃), arachidonate, the eicosanoids, and platelet activating factor. Individual glycerophospholipids can be viewed as stores of potential information released in response to cellular stimuli through the activation of specific enzymes. Messages are then carried by the released lipid-derived products in the form of specific interactions of these products with their targets [such as protein kinase C (PKC) or the IP₃ receptor].

Sphingolipids, which are structurally even more complex than the glycerophospholipids, also participate in signal transduction. Sphingolipids have roles in the response to cell contact, as receptor components, as anchors for proteins, and as markers of tumor progression and cell differentiation (2). Defects in several sphingolipid hydrolases result in the various forms of inherited sphingolipidoses (3). Sphingolipids also have an essential role in cell viability. In both *Saccharomyces cerevisiae* and

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mammalian cells, mutations in the first enzyme of de novo sphingolipid biosynthesis (serine-palmitoyl transferase) result in abolition of sphingolipid formation and loss of viability that is reconstituted by replacement with sphingolipids (4). Several bacterial hemolysins and cytotoxins have been identified as sphingomyelinases, and toxic fungal metabolites (such as the fumonisins, the sphingofungins, and the australifungins) specifically target enzymes of sphingolipid metabolism (5); these findings further underscore the importance of sphingolipids in cell regulation.

Sphingosine, sphingosine-1-phosphate, and possibly other lysosphingolipids have potential roles in signal transduction (2, 6). This role has been best defined, however, for sphingomyelin and ceramide. The following review focuses on recent developments in ceramide metabolism and physiology and their implications for aspects of cell biology such as apoptosis, growth suppression, and the stress response.

Generation, Kinetics, and Magnitude of the Ceramide Signal

A number of extracellular inducers of sphingomyelin hydrolysis, ceramide accumulation, or both have been identified. Among these inducers are 1,25-dihydroxyvitamin D₃, tumor necrosis factor- α (TNF- α), endotoxin, interferon- γ , interleukin-1 (IL-1), Fas ligands, CD28, dexamethasone, retinoic acid, progesterone, ionizing irradiation, chemotherapeutic agents, heat, and nerve growth factor (NGF) (7). Ceramide concentrations are also elevated in cells infected with human immunodeficiency virus (8) and in senescent fibroblasts (9).

The kinetics of ceramide formation in response to these inducers are complex and variable; reported responses range from seconds to hours, and the same inducer has generated very different ceramide responses in different studies. This range of findings has become a major source of confusion as to the possible relevant roles of ceramide in signal transduction and cell regulation. Figure 1 is an idealized conglomeration of the results of studies of ceramide accumulation in response to various agonists. From this scheme, at least three different categories of ceramide responses can be discerned.

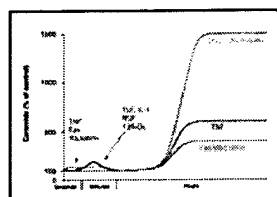


Fig. 1. Kinetics of ceramide formation. This is a composite scheme that illustrates three phases of ceramide formation (see text).
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Acute changes in ceramide concentration within seconds or within 1 to 2 min have been described primarily with TNF- α , ionizing radiation, and engagement of the Fas receptor (10). These changes may be indicative of a role for ceramide in mediating some of the very early responses to TNF- α , such as activation of nuclear factor κ B (NF- κ B). Such acute kinetics of ceramide are problematic for several reasons. First, the magnitude of the response has usually been modest, with increases on the order of 20 to 50% (Fig. 1). Second, these acute changes have not been detected in multiple other studies examining responses to TNF- α and Fas (11). Third, acute changes in ceramide (on the order of 50 to 100%) have been described that are caused by changes in culture conditions and exchange of media (12). Finally, the specificity of the ceramide effects implicated with these kinetics (for example,

activation of NF- κ B and Raf-1) has not been examined, which raises the distinct possibility that ceramide per se may not be the relevant lipid mediator in these responses.

Intermediate and reversible kinetics of ceramide accumulation have been best documented with IL-1, TNF- α , 1,25-dihydroxyvitamin D₃, NGF, and several neurotrophins (13) that cause accumulation of ceramide over 5 to 120 min in a reversible manner. The relevance of these responses--in which ceramide concentrations may double--is not readily apparent because they occur after the earliest responses to IL-1 and TNF- α , such as activation of NF- κ B.

Several extracellular stimuli and agents induce prolonged and persistent accumulation of ceramide that occurs over a period of several hours (Fig. 1). Serum withdrawal in leukemia cells results in a 15-fold accumulation of ceramide over 24 to 48 hours, and TNF- α and Fas activation also induce a three- to eightfold increase in intracellular concentrations of ceramide over 12 to 24 hours (11, 14). The magnitude of this response is more commensurate with cellular amounts of ceramides achieved when cells are exposed to exogenous short chain ceramides. This persistence of accumulation of ceramide raises the possibility of a reprogramming of cell function through a ceramide-activated pathway. Such a mechanism may be relevant to proposed roles for ceramide in growth suppression.

The sites of ceramide formation and the possible compartmentalization of signaling pools of sphingomyelin remain poorly understood. Sphingomyelin hydrolyzed in response to 1,25-dihydroxyvitamin D₃, NGF, or TNF- α is located in the plasma membrane (15), with several observations indicating localization on the inner leaflet. On the other hand, IL-1-induced sphingomyelin hydrolysis and ceramide formation colocalize with a caveolin-rich fraction. This pool of sphingomyelin resides on the outer leaflet of the plasma membrane (16). These studies underscore the possibility that distinct pools of sphingomyelin and ceramide exist and could participate in distinct pathways of cell regulation. No studies have examined the site of formation of the long and persistent phase of ceramide accumulation (Fig. 1).

Roles of Ceramide in Distinct Pathways of Cell Regulation

Recent discoveries have lent support to the principle that cells have intrinsic biochemical and molecular machinery that functions primarily to sense various forms of injury and insult and to execute appropriate programs of response. Mammalian cells respond to such stimuli primarily by undergoing cell cycle arrest to allow adequate time for repair of damage or by undergoing apoptosis (programmed cell death) if the damage is too severe and irreparable. It is also possible that other outcomes, such as terminal cell differentiation and senescence, represent a form of stress response.

Several lines of evidence suggest a role for ceramide in various forms of growth suppression and cell death. First, the spectrum of inducers of ceramide accumulation includes, and is perhaps limited to, most of the major inducers of apoptosis, terminal differentiation, or growth suppression. Growth factors do not appear to produce a similar response. Second, the changes in intracellular concentrations of ceramide in response to these extracellular agents precede the cellular effects of these agents on growth suppression. Third, treatment of cells with cell-permeable analogs of ceramide such as C2- and C6-ceramide has been shown to induce apoptosis, cell senescence, terminal differentiation, or cell cycle

arrest in several cell types (9, 14, 17). These effects of exogenous ceramides are specific to *D-erythro*-ceramide; *D-erythro*-dihydroceramide lacks any such activity. Dihydroceramide is a naturally occurring ceramide that lacks the 4-5 trans double bond but retains the stereochemical configuration of *D-erythro*-ceramide, and its uptake and metabolism are very similar to those of *D-erythro*-ceramide (18). Fourth, the cellular concentrations of C2- and C6-ceramide in cells exposed to 1 to 10 μ M C2- or C6-ceramide is approximately 10 to 100 pmol per nanomole of phospholipid, which is comparable to the concentrations of ceramide achieved after prolonged response to TNF- α or serum deprivation (Fig. 1). Finally, indirect manipulation of endogenous amounts of ceramide also supports a role for ceramide in mediating apoptosis and growth arrest. For example, the addition of precursor gangliosides, precursor sphingosine, bacterial sphingomyelinase (which generates ceramide at the plasma membrane), *D-threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) (which inhibits further incorporation of ceramide into glycolipids), or *D-erythro*-2-(*N*-myristoylamino)-1-phenyl-1-propanol (D-MAPP) (which inhibits ceramide metabolism through ceramidase) results in accumulation of ceramide ranging from three to eight times the concentrations in unstimulated cells (19). These increased concentrations are similar to those observed in cells treated with TNF, Fas, or dexamethasone, or in cells deprived of serum. In all these cases, the addition of these agents is accompanied by apoptosis, cell cycle arrest, or both.

Ceramide, growth suppression, and cell cycle arrest. In several cell lines, ceramides and inducers of ceramide formation cause inhibition of thymidine uptake and induce a G_0/G_1 cell cycle arrest that is accompanied by early dephosphorylation of the retinoblastoma gene product (Rb) (14, 19, 20) (Fig. 2). Several lines of evidence suggest a necessary role for Rb in mediating cell cycle arrest in response to ceramide. Cells deficient in Rb (such as cell lines derived from retinoblastoma tissues) do not manifest cell cycle arrest in response to ceramide. Cells that do respond to ceramide become unresponsive when Rb is inactivated or sequestered by any of several Rb-binding proteins such as adenoviral E1a and large T of SV40. On the other hand, the absence of Rb does not appear to diminish the responsiveness of cells to the apoptotic effects of ceramide. Ceramide-independent pathways for the regulation of Rb also exist. For example, as fibroblasts or MCF-7 breast cancer cells enter quiescence, Rb becomes dephosphorylated without concomitant changes in ceramide (Fig. 2). Thus, ceramide may be involved preferentially in stress-induced dephosphorylation of Rb.

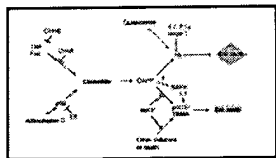


Fig. 2. Regulation of cell cycle arrest and apoptosis by ceramide. Various cytokines and extracellular agents (such as TNF and Fas) activate sphingomyelinases in a CrmA-inhibitable pathway. Other agents such as actinomycin D cause elevation of ceramide in a p53-dependent mechanism (55).

The accumulated ceramide activates CAPP, which then can result in activation of Rb, which in turn mediates the effects of ceramide on cell cycle arrest. Alternatively, ceramide can activate proteases of the prICE/YAMA family, resulting in apoptosis. Various viral proteins (indicated in red) appear to target several key components of this pathway. [View Larger Version of this Image (10K GIF file)]

In addition, ceramide suppresses the expression of the *c-myc* protooncogene by interfering with transcription elongation (21). Ceramide also inhibits the cellular activation of phospholipase D (22).

Because phospholipase D and its immediate and sequential products (phosphatidic acid and DAG, respectively) are implicated as either mitogenic or viability factors, these results indicate that ceramide not only activates growth suppressor programs but may also interfere with proliferative signaling pathways.

Ceramide, proteases, Bcl-2, and the apoptotic response. In several malignant and nonmalignant cell lines, ceramide rapidly and specifically induces apoptosis while closely related lipids remain inactive (17, 23). Ceramide activates proteases (24) of the interleukin converting enzyme (ICE) family, especially prICE/YAMA/ CPP32, the protease responsible for cleavage of poly- (adenosine diphosphate-ribose) polymerase (PARP). Activation of prICE by ceramide and induction of apoptosis are inhibited by overexpression of Bcl-2 (25, 26), which suggests that Bcl-2 functions downstream of ceramide. On the other hand, overexpression of Bcl-2 does not reduce the amounts of ceramide produced in response to extracellular agents (25) (Fig. 2). The effects of ceramide on prICE can be dissociated from activation of Rb, and vice versa (25); similarly, activation of PKC antagonizes the effects of ceramide on apoptosis but not on cell cycle arrest. Therefore, ceramide may relay a stress signal, whereby the specific cellular outcome (apoptosis or cell cycle arrest) appears to be determined by additional downstream modulators (such as Rb, Bcl-2, proteases, and PKC). Indeed, in some cell lines, ceramide may actually protect from apoptosis (27), possibly by preferentially steering cells into cell cycle arrest.

Other effects of ceramide. Although ceramide has been reported to activate the ERK1 and ERK2 members of the mitogen-activated protein (MAP) kinase family (28), the balance of current evidence suggests that ceramide may be more specifically coupled to stress-activated protein kinases (SAPK) and may even inhibit ERK1 and ERK2 (29). Addition of exogenous ceramides or sphingomyelinase to cells induces SAPK-dependent transcriptional activity through activation of c-Jun. A dominant negative mutant of SEK1, the protein kinase that phosphorylates and activates SAPK, interferes with ceramide-induced apoptosis (30), which suggests that SAPK functions downstream of ceramide in the cell death pathway. The relation of SAPK to Rb and death proteases (such as prICE/ CPP32) has not yet been determined.

Ceramide has an uncertain role in inducing the activity of NF- κ B. TNF- α may induce activation of an acidic sphingomyelinase, and the resulting ceramide has been suggested to activate NF- κ B (31). Exogenous ceramides have for the most part been shown not to induce nuclear translocation and activation of NF- κ B (32). In the only studies to show such an effect, the degree of stimulation of NF- κ B by ceramide was small relative to that observed with TNF- α (33). Also, ceramide appears not to induce transcription of NF- κ B-dependent genes (29). Other studies have also dissociated the ceramide response from NF- κ B activation (32, 34). For example, in cells treated with TNF- α , ceramide formation is not detected until after the induction of NF- κ B. Treatment of cells with PDMP, which increases intracellular concentrations of ceramide, does not cause activation of NF- κ B. Also, SR33557, an inhibitor of acid sphingomyelinase, does not inhibit TNF-induced activation of NF- κ B. Finally, in Niemann-Pick fibroblast cells that lack acid sphingomyelinase, NF- κ B is still activated in response to TNF- α and the effects of TNF- α on growth are preserved (35).

Ceramide may have a role in the regulation of protein secretion (36). Exogenously applied

C6-ceramide accumulates in the Golgi apparatus and interferes with the "constitutive" secretion of proteins, apolipoproteins, and triacylglycerol. The macrolide brefeldin A (BFA) induces sphingomyelin hydrolysis and mimics many of the cellular effects of exogenous ceramides, and exogenous ceramides bypass resistance to BFA. The effects of ceramide on protein secretion are opposed by okadaic acid and by phorbol ester activators of PKC, which suggests that protein secretion is under opposite regulation by modulators of protein kinases and phosphatases.

Other effects of ceramides include induction of differentiation of a number of cell types, including HL-60, glioma, and neuroblastoma cells ([13](#), [37](#)). Ceramide induces the transcription of cyclooxygenases 1 and 2 (COX) and α B-crystallin, a heat shock protein ([13](#), [38](#)). Ceramides have also been reported to inhibit esterification of cholesterol and to inhibit cytochrome P450 ([39](#)). In frog oocytes, ceramide triggers meiotic cell cycle progression ([40](#)).

Exogenous ceramides also stimulate the formation of prostaglandins and the release of IL-6 ([41](#)). The relative potency of various forms of ceramide in inducing these proinflammatory effects does not match that for the apoptotic effects (for example, *D-threo*-ceramide, which is an unnatural analog, is the most potent ceramide in inducing IL-6 secretion). This raises the possibility that molecules other than *D-erythro*-ceramide are the physiologic mediators of these effects.

Mechanisms of Ceramide Action

Biologically relevant and direct targets of ceramide should be activated by ceramide in vitro, and they should mediate the most proximal effects of ceramide in cells. There are three potential candidates for direct targets of ceramide action.

Ceramide-activated protein phosphatase (CAPP). In vitro, ceramide activates a serine-threonine protein phosphatase. This phosphatase is related to the PP2A family of phosphatases because it copurifies with the heterotrimeric form of PP2A and is inhibited potently by okadaic acid in vitro ([42](#)). It is also activated by ceramides with various N-linked acyl groups, but is not activated by other sphingolipids or neutral lipids. Studies in *S. cerevisiae* demonstrate that yeast CAPP is composed of the catalytic subunit encoded by *SIT4* and the regulatory subunits encoded by *CDC55* and *TPD3* ([43](#)).

Several lines of evidence suggest a role for CAPP in mediating at least some of the cellular activities of ceramide ([21](#), [42](#), [43](#), [44](#)). First, some of ceramide's effects on cells (such as apoptosis and down-regulation of the *c-myc* protooncogene) are inhibited by low concentrations of okadaic acid. Second, CAPP is activated in vitro by ceramide but not by dihydroceramide, which is inactive in eliciting ceramide effects on cells. Third, studies in *S. cerevisiae* show that yeast cells deficient in the various subunits of CAPP become resistant to the effects of ceramide. Further studies will be required to determine the relevant physiologic substrates for CAPP.

PKC ζ . Ceramide induces phosphorylation of PKC ζ in cells, and it activates the enzyme in vitro ([45](#)).

Ceramide-activated protein kinase (CAPK). CAPK is a membrane-associated kinase with a substrate specificity for serine or threonine in proximity to proline ([46](#)). Treatment of cells with sphingosine (but not C2-ceramide) results in a unique phosphorylation of Thr⁶⁶⁹ on the epidermal growth factor (EGF)

receptor, and C8-ceramide mimics the effects of sphingosine and EGF (47). In vitro, ceramide does not activate this kinase in a partially purified preparation, which raises the possibility that this kinase is not directly regulated by ceramide (48).

Regulation of Ceramide Formation

There are several possible sources of ceramide that accumulates in response to extracellular stimuli and agents of injury.

Sphingomyelinases. Current studies point to sphingomyelin as the major precursor for ceramide and to sphingomyelinase as the major enzyme responsible for ceramide generation. At least three distinct sphingomyelinases are implicated in distinct pathways. In HL-60 cells, 1,25-dihydroxyvitamin D₃ causes the activation of a Mg²⁺-independent sphingomyelinase, which is active at neutral pH. This enzyme has been purified, and its cytosolic localization and Mg²⁺ independence distinguish it from the Mg²⁺-dependent membrane sphingomyelinase (49).

A Mg²⁺-dependent membrane neutral sphingomyelinase is activated in response to TNF- α or serum deprivation (14). The temporal profile of its activation coincides with the major and delayed phase of ceramide accumulation, which suggests that it may participate in mediating the apoptotic and antiproliferative activities of TNF- α , Fas, 1- β -D-arabinofuranosylcytosine (Ara C), and other inducers of apoptosis. In HL-60 cells, arachidonate causes accumulation of ceramide and activation of the Mg²⁺-dependent sphingomyelinase in cell-free extracts (50). Because TNF- α activates phospholipase A2 (51), these studies may indicate that arachidonate (or one of its many products) is coupled to activation of neutral sphingomyelinase.

In addition, proteases are implicated in a pathway leading from TNF- α to the activation of sphingomyelinase (14, 52). Overexpression of CrmA (a viral protein that functions as a protease inhibitor with high affinity to ICE and related proteases) inhibits ceramide formation in response to TNF- α and protects cells from the cytotoxic action of TNF- α but not from that of ceramide. Reaper, a *Drosophila* gene product that causes cell death, results in ceramide formation that is abrogated by pharmacological inhibitors of ICE-like proteases. Acid sphingomyelinase has been proposed as a mediator of some of the activities of TNF- α , especially in the regulation of NF- κ B (31) as discussed in the previous section.

De novo synthesis. The de novo synthesis of ceramide is stimulated by retinoic acid, by the exchange of medium in tissue culture, and by the chemotherapeutic agent daunorubicin (12, 53). However, daunorubicin induces a biphasic response in sphingomyelin hydrolysis and ceramide generation, and fumonisins, an inhibitor of ceramide synthase, does not inhibit ceramide formation or apoptosis in response to daunorubicin (54).

Function of Ceramide as a Biostat

Unlike adenosine 3',5'-monophosphate (cyclic AMP), IP₃, phosphatidylinositol-3,4,5-trisphosphate (PIP₃), and many of the eicosanoids, ceramide and DAG do not function solely in signal transduction.

They are critical components in the intermediary metabolism of sphingolipids and glycerophospholipids. Also, the most pronounced changes in the amounts of ceramide and DAG occur over longer time frames than those seen with cyclic AMP, IP₃, or PIP₃. Therefore, ceramide may function more as a component of a "biostat" that measures and initiates responses to cellular stress, much as a thermostat measures and regulates temperature. For example, cellular concentrations of ceramide are increased by systemic stress (such as caused by TNF) or cell injury (such as from heat or chemotherapeutic agents). The cell then responds to these changes by undergoing apoptosis or growth arrest.

This concept of lipid biostats also offers a solution to the paradoxical dual function of ceramide and DAG as intermediary metabolites as well as second messengers and bioeffector molecules. Multiple enzymes are capable of regulating ceramide concentrations through distinct metabolic pathways (Fig. 3), and these individual enzymes may be activated by distinct stresses or extracellular agents. These enzymes may then serve to integrate the effects of several stimuli as a consequence of the regulation of ceramide concentrations. The ceramide concentrations would then reflect the effects of several stimuli and would serve as a gauge of the overall amount of stress or injury to which the cell has been exposed.

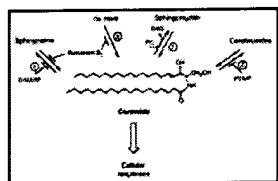


Fig. 3. Proposed role for ceramide and ceramide metabolism in the regulation of growth suppression. Ceramide plays a key role in sphingolipid metabolism, both as a key intermediate in sphingolipid metabolism and as a penultimate product in sphingolipid degradation. Various enzymes such as

sphingomyelinases (1), de novo pathways of ceramide formation (3), cerebrosidase (2), and ceramidase (4) may contribute to the regulation of ceramide concentrations. Therefore, it is proposed that various enzymes involved in ceramide metabolism can be potentially regulated in response to distinct classes of agents. The common effect of these pathways would be the accumulation of ceramide, which would then function as a biostat and launch various aspects of ceramide-mediated biology such as cell cycle arrest, cell senescence, or apoptosis.

[View Larger Version of this Image (13K GIF file)]

Studies of ceramide regulation and function, and more general studies of apoptosis and growth suppression, are beginning to define regulated pathways that ultimately function to deal with systemic as well as cellular stress and injury that may lead to cell cycle arrest, terminal differentiation, senescence, or apoptosis. Additional tools, such as inhibitors of specific enzymes of ceramide generation, are required to substantiate the hypotheses raised here. Understanding of these pathways may provide a basis for development of therapies to control cancer and inflammation.

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Volume 274, Number 5294, Issue of 13 Dec 1996, pp. 1855-1859.

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=> s screening method
L1 32998 SCREENING METHOD

=> s l1 and ehemothherapeutic agent
L2 0 L1 AND EHEMOTHERAPEUTIC AGENT

=> s l1 and chemotherapeutic agent
L3 52 L1 AND CHEMOTHERAPEUTIC AGENT

=> s l3 and sphingomyelinase
L4 1 L3 AND SPHINGOMYELINASE

=> d l4 cbib abs

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:593239 Document No. 135:134282 Method and identification of agents for
the modulation of acid-**sphingomyelinase**-related apoptosis.
Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1
20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707
19960726.

AB The present invention relates, first, to methods and compns. for the
modulation of acid **sphingomyelinase** (ASM)-related processes,
including apoptosis. Such apoptosis can include, but is not limited to,
environmental stress-induced apoptosis such as, for example, ionizing
radiation and/or **chemotherapeutic agent**-induced
apoptosis. Apoptosis can be characterized by a cellular morphol.
comprising cellular condensation, nuclear condensation or zeiosis. The
present invention further relates to methods for the identification of
compds. which modulate (i.e., either increase or decrease) sensitivity to
ASM-related processes, including apoptosis. ASM-deficient cell lines from
patients with Niemann-Pick disease and ASM-deficient mice were resistant
to radiation-induced apoptosis.

=> s l3 and ceramide
L5 1 L3 AND CERAMIDE

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-sphingomyelinase-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or **chemotherapeutic agent**-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

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L1 32998 S SCREENING METHOD
L2 0 S L1 AND EHEMOTHERAPEUTIC AGENT
L3 52 S L1 AND CHEMOTHERAPEUTIC AGENT
L4 1 S L3 AND SPHINGOMYELINASE
L5 1 S L3 AND CERAMIDE

=> s l1 and sphingomyelinase

L6 6 L1 AND SPHINGOMYELINASE

=> dup remove l6

PROCESSING COMPLETED FOR L6

L7 3 DUP REMOVE L6 (3 DUPLICATES REMOVED)

=> d l7 1-3 cbib abs

L7 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS

2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-**sphingomyelinase**-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the modulation of acid **sphingomyelinase** (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

L7 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

1999:184150 Document No. 130:205169 Method for treating a subject suffering from conditions associated with an extracellular zinc **sphingomyelinase**. Tabas, Ira; Schissel, Scott L.; Williams, Kevin Jon (The Trustees of Colombia University in the City of New York, USA). PCT Int. Appl. WO 9911283 A1 19990311, 189 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES,

FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18362 19980904. PRIORITY: US 1997-937234 19970905.

AB The present invention provides for a method for treating a subject suffering from a condition associated with an extracellular zinc **sphingomyelinase** activity which comprises administering to the subject an amount of a zinc **sphingomyelinase** inhibitor effective to decrease extracellular zinc **sphingomyelinase** activity in the subject and thereby treat the subject. The present invention also provides for a method for detecting whether a compound inhibits an activity of an extracellular zinc **sphingomyelinase** involving ceramide formation which comprises: (a) contacting a sample containing the zinc **sphingomyelinase** under acidic pH conditions known to be associated with the activity of such zinc **sphingomyelinase**, with: (i) a substrate of the zinc **sphingomyelinase** enzyme, and (ii) the compound being evaluated; (b) measuring the concentration of ceramide in the sample from (a); (c) detecting the amount of zinc **sphingomyelinase** activity in the sample based upon the concentration of ceramide measured in step (b); and (d) comparing the amount of **sphingomyelinase** activity determined in step (c) with the amount of **sphingomyelinase** activity determined in the absence of the compound, to determine whether the compound inhibits the activity of zinc **sphingomyelinase**.

L7 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
81074020 EMBASE Document No.: 1981074020. A **screening method** for bacterial production of **sphingomyelinase**. Malmqvist T.. Dept. Bacteriol., Karolinska Inst., S-104 01 Stockholm, Sweden. FEMS Microbiology Letters 10/1 (91-94) 1981. CODEN: FMLED7. Pub. Country: Netherlands. Language: English.

AB This report describes a specific method for screening for **sphingomyelinase** production by bacteria. The presumptive positive findings obtained with staphylococci isolated from clinical specimens in this screening test was compared with quantitative determinations of their sphingomyelinase production when grown in nutrient broth. Enzyme activity was measured by specific hydrolysis of immobilized sphingomyelin and by haemolytic titration on sheep erythrocytes.

=> s l1 and ceramide
3 FILES SEARCHED...

L8 5 L1 AND CERAMIDE

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PROCESSING COMPLETED FOR L8
L9 5 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-5 cbib abs

L9 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:798284 Document No. 135:352747 G protein-coupled receptor (GPCR) agonists and antagonists, and methods of activating and inhibiting GPCR using them. Kuliopulos, Athan; Covic, Lidija (New England Medical Center, USA). PCT Int. Appl. WO 2001081408 A2 20011101, 60 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US13063

20010423. PRIORITY: US 2000-PV198993 20000421.

AB The invention relates generally to G protein coupled receptors and in particular to agonists and antagonists of G protein receptors and methods of using them. Methods for identification of potential therapeutic agents and treating GPCR-assocd. pathol. are also disclosed.

L9 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2002 ACS

2001:677067 Document No. 135:251931 Function homology **screening method**, and use in identification of drug candidates. Berg, Ellen L.; Butcher, Eugene C.; Melrose, Jennifer; Plavec, Ivan (Bioseek, Inc., USA). PCT Int. Appl. WO 2001067103 A1 20010913, 128 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US7190 20010306. PRIORITY: US 2000-PV186976 20000306; US 2000-PV195672 20000407.

AB A method is provided for screening biol. active agents based on the anal. of complex biol. responses in culture. Methods for selecting cells and culture conditions for such screens are provided, as well as the identification of an optimized set of discrete parameters to be measured, and the use of biomap anal. for rapid identification and characterization of drug candidates, genetic sequences acting pathways, and the like. A feature of the invention is simultaneous screening of a large no. of cellular pathways, and the rapid identification of compds. that cause cellular responses.

L9 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS

2001:208507 Document No. 134:234000 Spatially-addressed lipid bilayer arrays and lipid bilayers with addressable confined aqueous compartments. Cremer, Paul S.; Simanek, Eric E.; Yang, Tinglu (The Texas A & M University System, USA). PCT Int. Appl. WO 2001020330 A1 20010322, 87 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US25627 20000918. PRIORITY: US 1999-PV154576 19990917; US 2000-564708 20000504.

AB Disclosed are spatially-addressed arrays of discreet fluid lipid bilayers prepd. by flexible patterning methods that facilitate the compartmentalization of lipid membranes and aq. solns. disposed thereon into discreet, spatially-addressable, microarray partitions, onto specific and discreet locations of a substantially planar solid support. This process can either be used in parallel or sequentially to pattern thousands of distinct membranes on a single "biochip", and to assay pluralities of selected analyte components contacted with the discreet lipid bilayer compartments for one or more target mols. Also provided are biochip microarray systems and methods for their prodn. that comprise arrays of confined aq. compartments disposed upon such compartmentalized lipid bilayers. The aq. compartments are independently addressable, thereby facilitating reagent delivery, reagent extn., anal. probe and high-throughput analyte **screening methods**.

L9 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS

2001:593239 Document No. 135:134282 Method and identification of agents for the modulation of acid-sphingomyelinase-related apoptosis. Kolesnick, Richard; Schuchman, Edward H. (USA). U.S. US 6274309 B1 20010814, 21 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-687707 19960726.

AB The present invention relates, first, to methods and compns. for the

modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphol. comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compds. which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis. ASM-deficient cell lines from patients with Niemann-Pick disease and ASM-deficient mice were resistant to radiation-induced apoptosis.

L9 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS

1999:184150 Document No. 130:205169 Method for treating a subject suffering from conditions associated with an extracellular zinc sphingomyelinase. Tabas, Ira; Schissel, Scott L.; Williams, Kevin Jon (The Trustees of Colombia University in the City of New York, USA). PCT Int. Appl. WO 9911283 A1 19990311, 189 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18362 19980904. PRIORITY: US 1997-937234 19970905.

AB The present invention provides for a method for treating a subject suffering from a condition assocd. with an extracellular zinc sphingomyelinase activity which comprises administering to the subject an amt. of a zinc sphingomyelinase inhibitor effective to decrease extracellular zinc sphingomyelinase activity in the subject and thereby treat the subject. The present invention also provides for a method for detg. whether a compd. inhibits an activity of an extracellular zinc sphingomyelinase involving **ceramide** formation which comprises: (a) contacting a sample contg. the zinc sphingomyelinase under acidic pH conditions known to be assocd. with the activity of such zinc sphingomyelinase, with: (i) a substrate of the zinc sphingomyelinase enzyme, and (ii) the compd. being evaluated; (b) measuring the concn. of **ceramide** in the sample from (a); (c) detg. the amt. of zinc sphingomyelinase activity in the sample based upon the concn. of **ceramide** measured in step (b); and (d) comparing the amt. of sphingomyelinase activity detd. in step (c) with the amt. of sphingomyelinase activity detd. in the absence of the compd., to det. whether the compd. inhibits the activity of zinc sphingomyelinase.

=> s kolesnick r?/au or schuchman e?/au
L10 962 KOLESNICK R?/AU OR SCHUCHMAN E?/AU

=> s k10 and sphingomyelinase
L11 5 K10 AND SPHINGOMYELINASE

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12 1 DUP REMOVE L11 (4 DUPLICATES REMOVED)

=> d l12 cbib abs

L12 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
2001017223 Document Number: 20453360. PubMed ID: 10998148. Impaired cutaneous permeability barrier function, skin hydration, and **sphingomyelinase** activity in keratin 10 deficient mice. Jensen J M; Schutze S; Neumann C; Proksch E. (Department of Dermatology and Institute of Immunology, University of Kiel, Germany.) JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2000 Oct) 115 (4) 708-13. Journal code: IHZ.

ISSN: 0022-202X. Pub. country: United States. Language: English.
AB Point mutations in the suprabasal cytokeratins 1 (K1) or 10 (K10)
) in humans have been shown to be the cause of the congenital ichthyosis
epidermolytic hyperkeratosis. Recently, a K10 deficient mouse
model was established serving as a model for epidermolytic hyperkeratosis.
Homozygotes suffered from severe skin fragility and died shortly after
birth. Heterozygotes developed hyperkeratosis with age. To see whether
phenotypic abnormalities in the mouse model were associated with changes
in skin barrier function and skin water content we studied basal
transepidermal water loss and capacity for barrier repair after
experimental barrier disruption as well as stratum corneum hydration.
Also, we determined the activities of acid and neutral
sphingomyelinase key enzymes of the tumor necrosis factor and
interleukin-1 signal transduction pathways generating the ceramides most
important for epidermal permeability barrier homeostasis. Neonatal
homozygotes showed an 8-fold increase in basal transepidermal water loss
compared with wild type controls. Adult heterozygotes exhibited delayed
barrier repair after experimental barrier disruption. Stratum corneum
hydration was reduced in homozygous and heterozygous mice. Acid
sphingomyelinase activity, which is localized in the epidermal
lamellar bodies and generates ceramides for extracellular lipid lamellae
in the stratum corneum permeability barrier, was reduced in homozygous as
well as heterozygous animals. Neutral **sphingomyelinase** activity,
which has a different location and generates ceramides involved in cell
signaling, was increased. The reduction in acid **sphingomyelinase**
activity may explain the recently described decreased ratio of ceramides
to total lipids in K10 deficient mice. In summary, our results
demonstrate the crucial role of the keratin filament for permeability
barrier function and stratum corneum hydration.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:30:53 ON
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L1 32998 S SCREENING METHOD
L2 0 S L1 AND CHEMOTHERAPEUTIC AGENT
L3 52 S L1 AND CHEMOTHERAPEUTIC AGENT
L4 1 S L3 AND SPHINGOMYELINASE
L5 1 S L3 AND CERAMIDE
L6 6 S L1 AND SPHINGOMYELINASE
L7 3 DUP REMOVE L6 (3 DUPLICATES REMOVED)
L8 5 S L1 AND CERAMIDE
L9 5 DUP REMOVE L8 (0 DUPLICATES REMOVED)
L10 962 S KOLESNICK R?/AU OR SCHUCHMAN E?/AU
L11 5 S K10 AND SPHINGOMYELINASE
L12 1 DUP REMOVE L11 (4 DUPLICATES REMOVED)

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L13 449 L10 AND CERAMIDE

=> s l13 and screening compound

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=> s l15 and chemotherapeutics

L16 0 L15 AND CHEMOTHERAPEUTICS

=> s l15 and apoptosis

1 FILES SEARCHED...

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L17 79 L15 AND APOPTOSIS

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L18 79 DUP REMOVE L17 (0 DUPLICATES REMOVED)

=> s l18 and sphingomyelinase
3 FILES SEARCHED...
L19 33 L18 AND SPHINGOMYELINASE

=> s l19 and ceramide
L20 33 L19 AND CERAMIDE

=> d l20 1-22 cbib abs

L20 ANSWER 1 OF 33 MEDLINE
2001434346 Document Number: 21214818. PubMed ID: 11313707. Niemann-Pick Disease versus acid **sphingomyelinase** deficiency. Lozano J; Morales A; Cremesti A; Fuks Z; Tilly J L; **Schuchman E**; Gulbins E; **Kolesnick R**. CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 100-3. Journal code: C7U; 9437445. ISSN: 1350-9047. Pub. country: England: United Kingdom. Language: English.

L20 ANSWER 2 OF 33 MEDLINE
2001376289 Document Number: 21316440. PubMed ID: 11287428. **Ceramide** enables fas to cap and kill. Cremesti A; Paris F; Grassme H; Holler N; Tschopp J; Fuks Z; Gulbins E; **Kolesnick R**. (Laboratory of Signal Transduction and Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 29) 276 (26) 23954-61. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Recent studies suggest that trimerization of Fas is insufficient for **apoptosis** induction and indicate that super-aggregation of trimerized Fas might be prerequisite. For many cell surface receptors, cross-linking by multivalent ligands or antibodies induces their lateral segregation within the plasma membrane and co-localization into "caps" on one pole of the cell. In this study, we show that capping of Fas is essential for optimal function and that capping is **ceramide** -dependent. In Jurkat T lymphocytes and in primary cultures of hepatocytes, **ceramide** elevation was detected as early as 15-30 s and peaked at 1 min after CH-11 and Jo2 anti-Fas antibody treatment, respectively. Capping was detected 30 s after Fas ligation, peaked at 2 min, and was maintained at a lower level for as long as 30 min in both cell types. **Ceramide** generation appeared essential for capping. Acid **sphingomyelinase** -/- hepatocytes were defective in Jo2-induced **ceramide** generation, capping, and **apoptosis** , and nanomolar concentrations of C(16)-**ceramide** restored these events. To further explore the role of **ceramide** in capping of Fas, we employed FLAG-tagged soluble Fas ligand (sFasL), which binds trimerized Fas but is unable to induce capping or **apoptosis** in Jurkat cells. Cross-linking of sFasL with M2 anti-FLAG antibody induced both events. Pretreatment of cells with natural C(16)-**ceramide** bypassed the necessity for forced antibody cross-linking and enabled sFasL to cap and kill. The presence of intact sphingolipid-enriched membrane domains may be essential for Fas capping since their disruption with cholesterol-depleting agents abrogated capping and prevented **apoptosis**. These data suggest that capping is a **ceramide** -dependent event required for optimal Fas signaling in some cells.

L20 ANSWER 3 OF 33 MEDLINE
2001342203 Document Number: 21282993. PubMed ID: 11279185. CD95 signaling via **ceramide**-rich membrane rafts. Grassme H; Jekle A; Riehle A; Schwarz H; Berger J; Sandhoff K; **Kolesnick R**; Gulbins E.

(Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 8) 276 (23) 20589-96. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

- AB Clustering seems to be employed by many receptors for transmembrane signaling. Here, we show that acid **sphingomyelinase** (ASM)-released **ceramide** is essential for clustering of CD95. In vitro and in vivo, extracellularly orientated **ceramide**, released upon CD95-triggered translocation of ASM to the plasma membrane outer surface, enabled clustering of CD95 in sphingolipid-rich membrane rafts and **apoptosis** induction. Whereas ASM deficiency, destruction of rafts, or neutralization of surface **ceramide** prevented CD95 clustering and **apoptosis**, natural **ceramide** only rescued ASM-deficient cells. The data suggest CD95-mediated clustering by **ceramide** is prerequisite for signaling and death.

L20 ANSWER 4 OF 33 MEDLINE

2001331477 Document Number: 21292405. PubMed ID: 11399033. An enzymatic assay for quantifying sphingomyelin in tissues and plasma from humans and mice with Niemann-Pick disease. He X; Chen F; Gatt S; **Schuchman E H.** (Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.) ANALYTICAL BIOCHEMISTRY, (2001 Jun 15) 293 (2) 204-11. Journal code: 4NK; 0370535. ISSN: 0003-2697. Pub. country: United States. Language: English.

- AB Sphingomyelin is an important lipid component of cell membranes and lipoproteins which can be hydrolyzed by **sphingomyelinases** into **ceramide** and phosphorylcholine. The type A and B forms of Niemann-Pick disease (NPD) are lipid storage disorders due to the deficient activity of the enzyme acid **sphingomyelinase**, and the resultant accumulation of sphingomyelin in cells and tissues. In this paper we report a new, enzyme-based method to quantify the levels of sphingomyelin in tissues and plasma of normal individuals and NPD patients. The method utilizes **sphingomyelinase** from *Bacillus cereus* to completely hydrolyze the sphingomyelin into **ceramide**. Quantification of the sphingomyelin-derived **ceramide** is accomplished using *Escherichia coli* diacylglycerol (DAG) kinase and [γ -(32)P]ATP. The resulting [(32)P]**ceramide** is quantified using a phosphor-imager system following TLC separation. This procedure allowed quantification of sphingomyelin over a broad range from 10 pmol to 1 nmol. To validate this assay we quantified sphingomyelin in plasma and tissues obtained from normal and NPD mice and humans. The sphingomyelin content in adult homozygous (-/-) or heterozygous (+/-) NPD mouse plasma was significantly elevated compared to that of normal mice (up to twofold). Moreover, the accumulated sphingomyelin in the tissues of NPD mice was 4 to 40 times higher than that in normal mice depending on the tissue analyzed. The sphingomyelin levels in plasma from several type B NPD patients also were significantly elevated compared to normal individuals of the same age. Based on these results we propose that this new, enzyme-based procedure can provide sensitive and reproducible sphingomyelin quantification in tissues and fluids from normal individuals and NPD patients. It could be a useful tool for the diagnosis of NPD and the evaluation of NPD treatment protocols, as well as for the study of **ceramide**-mediated **apoptosis** since the method provides the simultaneous determination of sphingomyelin and **ceramide** in the same lipid extract. Copyright 2001 Academic Press.

L20 ANSWER 5 OF 33 MEDLINE

2001290716 Document Number: 21269394. PubMed ID: 11096096. Natural **ceramide** reverses Fas resistance of acid **sphingomyelinase** (-/-) hepatocytes. Paris F; Grassme H; Cremesti A; Zager J; Fong Y; Haimovitz-Friedman A; Fuks Z; Gulbins E; **Kolesnick R.** (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Mar 16) 276 (11) 8297-305. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The role of the second messenger **ceramide** in Fas-mediated death requires clarification. To address this issue, we generated hepatocytes from paired acid **sphingomyelinase** (ASMase; *asmase*) (+/+) and *asmase*(-/-) mice. *asmase*(-/-) hepatocytes, derived from 8-week-old mice, manifested normal sphingomyelin content and normal morphological, biochemical, and biologic features. Nonetheless, ASMase-deficient hepatocytes did not display rapid **ceramide** elevation or **apoptosis** in response to Jo2 anti-Fas antibody. *asmase*(-/-) hepatocytes were not inherently resistant to **apoptosis** because staurosporine, which did not induce early **ceramide** elevation, stimulated a normal apoptotic response. The addition of low nanomolar quantities of natural C16-**ceramide**, which by itself did not induce **apoptosis**, completely restored the apoptotic response to anti-Fas in *asmase*(-/-) hepatocytes. Other sphingolipids did not replace natural **ceramide** and restore Fas sensitivity. Overcoming resistance to Fas in *asmase*(-/-) hepatocytes by natural **ceramide** is evidence that it is the lack of **ceramide** and not ASMase which determines the apoptotic phenotype. The ability of natural **ceramide** to rescue the phenotype without reversing the genotype provides evidence that **ceramide** is obligate for Fas induction of **apoptosis** in hepatocytes.

L20 ANSWER 6 OF 33 MEDLINE

2001213898 Document Number: 21115301. PubMed ID: 11220788. Pivotal role for acidic **sphingomyelinase** in cerebral ischemia-induced **ceramide** and cytokine production, and neuronal **apoptosis**. Yu Z F; Nikolova-Karakashian M; Zhou D; Cheng G; Schuchman E H; Mattson M P. (Sanders-Brown Research Center on Aging, University of Kentucky, Lexington 40536, USA.) JOURNAL OF MOLECULAR NEUROSCIENCE, (2000 Oct) 15 (2) 85-97. Journal code: AVM; 9002991. ISSN: 0895-8696. Pub. country: United States. Language: English.

AB Stroke is a major cause of long-term disability, the severity of which is directly related to the numbers of neurons that succumb to the ischemic insult. The signaling cascades activated by cerebral ischemia that may either promote or protect against neuronal death are not well understood. One injury-responsive signaling pathway that has recently been characterized in studies of non-neural cells involves cleavage of membrane sphingomyelin by acidic and/or neutral **sphingomyelinase** (ASMase) resulting in generation of the second messenger **ceramide**. We now report that transient focal cerebral ischemia induces large increases in ASMase activity, **ceramide** levels, and production of inflammatory cytokines in wild-type mice, but not in mice lacking ASMase. The extent of brain tissue damage is decreased and behavioral outcome improved in mice lacking ASMase. Neurons lacking ASMase exhibit decreased vulnerability to excitotoxicity and hypoxia, which is associated with decreased levels of intracellular calcium and oxyradicals. Treatment of mice with a drug that inhibits ASMase activity and **ceramide** production reduces ischemic neuronal injury and improves behavioral outcome, suggesting that drugs that inhibit this signaling pathway may prove beneficial in stroke patients.

L20 ANSWER 7 OF 33 MEDLINE

2001112676 Document Number: 20576386. PubMed ID: 11031259. Cell autonomous **apoptosis** defects in acid **sphingomyelinase** knockout fibroblasts. Lozano J; Menendez S; Morales A; Ehleiter D; Liao W C; Wagman R; Haimovitz-Friedman A; Fuks Z; Kolesnick R. (Laboratory of Signal Transduction and Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jan 5) 276 (1) 442-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB A body of evidence suggests that stress-induced sphingomyelin hydrolysis to the second messenger **ceramide** initiates **apoptosis** in some cells. Although studies using lymphoblasts from Niemann-Pick disease patients or acid **sphingomyelinase** (ASMase)-deficient

mice have provided genetic support for this hypothesis, these models have not been universally accepted as definitive. Here, we show that mouse embryonic fibroblasts (MEFs) prepared from *asmase* mice manifest cell autonomous defects in **apoptosis** in response to several stresses. In particular, *asmase*(-/-) MEFs failed to generate **ceramide** and were totally resistant to radiation-induced **apoptosis** but remained sensitive to staurosporine, which did not induce **ceramide**. *asmase*(-/-) MEFs were also partially resistant to tumor necrosis factor alpha/ actinomycin D and serum withdrawal. Thus, resistance to **apoptosis** in *asmase*(-/-) MEFs was not global but rather stress type specific. Most importantly, the sensitivity to stress could be restored in the *asmase*(-/-) MEFs by administration of natural **ceramide**. Overcoming **apoptosis** resistance by natural **ceramide** is evidence that it is the lack of **ceramide**, not *ASMase*, that determines **apoptosis** sensitivity. The ability to rescue the apoptotic phenotype without reversing the genotype by the product of the enzymatic deficiency provides proof that **ceramide** is obligate for **apoptosis** induction in response to some stresses.

L20 ANSWER 8 OF 33 MEDLINE

2000187582 Document Number: 20187582. PubMed ID: 10722706. Role of acidic **sphingomyelinase** in Fas/CD95-mediated cell death. Lin T; Genestier L; Pinkoski M J; Castro A; Nicholas S; Mogil R; Paris F; Fuks Z; **Schuchman E H; Kolesnick R N**; Green D R. (Department of Cellular Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California 92121, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8657-63. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Engagement of the Fas receptor has been reported to induce **ceramide** generation via activation of acidic **sphingomyelinase** (*aSMase*). However, the role of *aSMase* in Fas-mediated cell death is controversial. Using genetically engineered mice deficient in the *aSMase* gene (*aSMase*(-/-)), we found that thymocytes, concanavalin A-activated T cells, and lipopolysaccharide-activated B cells derived from both *aSMase*(-/-) and *aSMase*(+/+) mice were equally sensitive to Fas-mediated cell death, triggered by either anti-Fas antibody or Fas ligand in vitro. Similarly, activation-induced **apoptosis** of T lymphocytes was unaffected by the status of *aSMase*, and *aSMase*(-/-) mice failed to show immunological symptoms seen in animals with defects in Fas function. In vivo, intravenous injection of 3 microg/25 g mouse body weight of anti-Fas Jo2 antibody into *aSMase*(-/-) mice failed to affect hepatocyte **apoptosis** or mortality, whereas massive hepatocyte **apoptosis** and animal death occurred in wild type littermates. Animals heterozygous for *aSMase* deficiency were also significantly protected. Susceptibility of *aSMase*(-/-) mice to anti-Fas antibody was demonstrated with higher antibody doses (>=4 microg/25 g mouse). These data indicate a role for *aSMase* in Fas-mediated cell death in some but not all tissues.

L20 ANSWER 9 OF 33 MEDLINE

2000129045 Document Number: 20129045. PubMed ID: 10667583. Radiation-induced **apoptosis** of endothelial cells in the murine central nervous system: protection by fibroblast growth factor and **sphingomyelinase** deficiency. Pena L A; Fuks Z; **Kolesnick R N**. (Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) CANCER RESEARCH, (2000 Jan 15) 60 (2) 321-7. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Injury to the central nervous system (CNS) by ionizing radiation may be a consequence of damage to the vascular endothelium. Recent studies showed that radiation-induced **apoptosis** of endothelial cells in vitro and in the lung in vivo is mediated by the lipid second messenger **ceramide** via activation of acid **sphingomyelinase** (*ASM*). This apoptotic response to radiation can be inhibited by basic fibroblast

growth factor or by genetic mutation of ASM. In the CNS, single-dose radiation has been shown to result in a 15% loss of endothelial cells within 24 h, but whether or not this loss is associated with **apoptosis** remains unknown. In the present studies, dose- and time-dependent induction of **apoptosis** was observed in the C57BL/6 mouse CNS. **Apoptosis** was quantified by terminal deoxynucleotidyl transferase-mediated nick end labeling, and specific endothelial **apoptosis** was determined by histochemical double labeling with terminal deoxynucleotidyl transferase-mediated nick end labeling and Lycopersicon esculentum lectin. Beginning at 4 h after single-dose radiation, **apoptosis** was ongoing for 24 h and peaked at 12 h at an incidence of 0.7-1.4% of the total cells in spinal cord sections. Up to 20% of the apoptotic cells were endothelial. This effect was also seen in multiple regions of the brain (medulla, pons, and hippocampus). A significant reduction of radiation-induced **apoptosis** was observed after i.v. basic fibroblast growth factor treatment (0.45-4.5 microg/mouse). Identical results were noted in C3H/HeJ mice. Furthermore, irradiated ASM knockout mice displayed as much as a 70% reduction in endothelial **apoptosis**. This study demonstrates that ionizing radiation induces early endothelial cell **apoptosis** throughout the CNS. These data are consistent with recent evidence linking radiation-induced stress with **ceramide** and suggest approaches to modify the apoptotic response in control of radiation toxicity in the CNS.

L20 ANSWER 10 OF 33 MEDLINE

1999114028 Document Number: 99114028. PubMed ID: 9916990. Stress signals for **apoptosis**: **ceramide** and c-Jun kinase. Basu S; Kolesnick R. (Laboratory of Signal Transduction, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) ONCOGENE, (1998 Dec 24) 17 (25) 3277-85. Ref: 75. Journal code: ONC; 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mammalian systems respond to environmental stress by either adapting or undergoing programmed cell death. While there is general agreement that the caspase family of proteases serve as the effectors of the apoptotic death response, the signaling apparatus involved in the decision to activate the caspase system is less clear. In the past few years, the sphingomyelin and c-Jun Kinase (JNK)/Stress-activated Protein Kinase (SAPK) pathways have been linked to the death response in many cellular systems. These signaling systems are found throughout the animal kingdom, and **ceramide** signaling is conserved through yeast. Since yeast do not undergo **apoptosis**, the sphingomyelin pathway appears evolutionarily older than the caspase-mediated death programs. While recent reviews by several groups have broadly surveyed **ceramide** signaling in **apoptosis**, this paper examines the role of **sphingomyelinases** and the JNK/SAPK pathway in coordinate signaling of **apoptosis**.

L20 ANSWER 11 OF 33 MEDLINE

1998441840 Document Number: 98441840. PubMed ID: 9769704. Signaling in and regulation of ionizing radiation-induced **apoptosis** in endothelial cells. Billis W; Fuks Z; Kolesnick R. (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) RECENT PROGRESS IN HORMONE RESEARCH, (1998) 53 85-92; discussion 93. Ref: 29. Journal code: R1D; 0404471. ISSN: 0079-9963. Pub. country: United States. Language: English.

AB Exposure of mammalian cells to ionizing radiation leads primarily to DNA damage-induced cell death. The induction of **apoptosis** by ionizing radiation represents an alternative mode to cell kill. Breakdown of sphingomyelin to produce **ceramide** by activation of **sphingomyelinase** is one of the upstream signalling cascades activated in apoptotic cells in response to stimuli such as TNF. Using genetic models of acid **sphingomyelinase** deficiency, the **ceramide** generated by radiation-induced activation of **sphingomyelinase** has been shown to serve as a second messenger in

initiating an apoptotic response. PKC activation represents an upstream anti-apoptotic checkpoint at the **sphingomyelinase** level as well as a checkpoint downstream of **ceramide** generation. The balance between these pro- and anti-apoptotic systems may determine the magnitude of the observed apoptotic response.

L20 ANSWER 12 OF 33 MEDLINE

1998266812 Document Number: 98266812. PubMed ID: 9605775.

12-O-tetradecanoylphorbol-13-acetate-induced **apoptosis** in LNCaP cells is mediated through **ceramide** synthase. Garzotto M; White-Jones M; Jiang Y; Ehleiter D; Liao W C; Haimovitz-Friedman A; Fuks Z; **Kolesnick R.** (Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.) CANCER RESEARCH, (1998 May 15) 58 (10) 2260-4. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Protein kinase C (PKC) activation is often antiapoptotic, although in a few cell types PKC initiates **apoptosis** by an unknown mechanism. Recent investigations showed that activation of PKC alpha by 12-O-tetradecanoylphorbol 13-acetate (TPA) induced **apoptosis** in LNCaP prostate cancer cells. The present studies examine the mechanism of this effect and show that de novo **ceramide** generation through the enzyme **ceramide** synthase is required. TPA induced rapid **ceramide** generation, which was detectable by 1 h and increased linearly for 12 h. TPA-induced **apoptosis** was measurable by 12 h and was progressive for 48 h. Investigations into the mechanism of TPA-induced **ceramide** generation revealed that acid and neutral **sphingomyelinase** activities were not enhanced. However, TPA induced an increase in **ceramide** synthase activity that persisted for at least 16 h. Treatment with fumonisin B1, a specific natural inhibitor of **ceramide** synthase, abrogated both **ceramide** production and TPA-induced **apoptosis**. **Ceramide** analogues bypassed fumonisin B1 inhibition to initiate **apoptosis** directly. Thus, **ceramide** appears to be a necessary signal for TPA-induced **apoptosis** in LNCaP cells. This represents the first description of a pathway by which PKC may signal **apoptosis**.

L20 ANSWER 13 OF 33 MEDLINE

1998167926 Document Number: 98167926. PubMed ID: 9500792. Acidic

sphingomyelinase (ASM) is necessary for fas-induced GD3 ganglioside accumulation and efficient **apoptosis** of lymphoid cells. De Maria R; Rippo M R; **Schuchman E H**; Testi R. (Department of Experimental Medicine and Biochemical Sciences, University of Rome "Tor Vergata," 00133 Rome, Italy.) JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Mar 16) 187 (6) 897-902. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB **Ceramides** deriving from sphingomyelin hydrolysis are important mediators of apoptotic signals originating from Fas (APO-1/CD95). However, definitive evidence for the role played by individual **sphingomyelinases** is still lacking. We have analyzed lymphoblastoid cell lines derived from patients affected by Niemann Pick disease (NPD), an autosomal recessive disorder caused by loss-of-function mutations within the acidic **sphingomyelinase** (ASM) gene. NPD lymphoblasts, which display normal neutral **sphingomyelinase** activity, fail to activate ASM in response to Fas cross-linking, unlike normal lymphoblasts. NPD lymphoblasts also fail to accumulate GD3 ganglioside, a downstream mediator of **ceramide**-induced cell death (De Maria, R., L. Lenti, F. Malisan, F. D'Agostino, B. Tomassini, A. Zeuner, M.R. Rippo, R. Testi. 1997. Science. 277:1652-1655), and display a substantially inefficient **apoptosis** after Fas cross-linking. Inefficient **apoptosis** is due to lack of ASM activity, because proximal signaling from Fas in NPD lymphoblasts is not impaired and **apoptosis** can be efficiently triggered by passing the ASM defect with exogenous **ceramides**. Moreover, mannose receptor-mediated transfer of ASM into NPD lymphoblasts rescues their ability to transiently activate ASM, accumulate GD3, and rapidly undergo **apoptosis**.

after Fas cross-linking. These results provide definitive genetic evidence for the role of ASM in the progression of apoptotic signals originating from Fas.

L20 ANSWER 14 OF 33 MEDLINE

1998044248 Document Number: 98044248. PubMed ID: 9382882.

Lipopolysaccharide induces disseminated endothelial **apoptosis** requiring **ceramide** generation. Haimovitz-Friedman A; Cordon-Cardo C; Bayoumy S; Garzotto M; McLoughlin M; Gallily R; Edwards C K 3rd; **Schuchman E H**; Fuks Z; **Kolesnick R**. (Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York 10021, USA.) JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Dec 1) 186 (11) 1831-41. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The endotoxic shock syndrome is characterized by systemic inflammation, multiple organ damage, circulatory collapse and death. Systemic release of tumor necrosis factor (TNF)-alpha and other cytokines purportedly mediates this process. However, the primary tissue target remains unidentified. The present studies provide evidence that endotoxic shock results from disseminated endothelial **apoptosis**. Injection of lipopolysaccharide (LPS), and its putative effector TNF-alpha, into C57BL/6 mice induced **apoptosis** in endothelium of intestine, lung, fat and thymus after 6 h, preceding nonendothelial tissue damage. LPS or TNF-alpha injection was followed within 1 h by tissue generation of the pro-apoptotic lipid **ceramide**. TNF-binding protein, which protects against LPS-induced death, blocked LPS-induced **ceramide** generation and endothelial **apoptosis**, suggesting systemic TNF is required for both responses. Acid **sphingomyelinase** knockout mice displayed a normal increase in serum TNF-alpha in response to LPS, yet were protected against endothelial **apoptosis** and animal death, defining a role for **ceramide** in mediating the endotoxic response. Furthermore, intravenous injection of basic fibroblast growth factor, which acts as an intravascular survival factor for endothelial cells, blocked LPS-induced **ceramide** elevation, endothelial **apoptosis** and animal death, but did not affect LPS-induced elevation of serum TNF-alpha. These investigations demonstrate that LPS induces a disseminated form of endothelial **apoptosis**, mediated sequentially by TNF and **ceramide** generation, and suggest that this cascade is mandatory for evolution of the endotoxic syndrome.

L20 ANSWER 15 OF 33 MEDLINE

97267750 Document Number: 97267750. PubMed ID: 9113079. Stress-induced **apoptosis** and the sphingomyelin pathway. Pena L A; Fuks Z; **Kolesnick R**. (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) BIOCHEMICAL PHARMACOLOGY, (1997 Mar 7) 53 (5) 615-21. Ref: 63. Journal code: 9Z4; 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The sphingomyelin pathway is a ubiquitous, evolutionarily conserved signaling system initiated by hydrolysis of the plasma membrane phospholipid sphingomyelin to generate the second messenger **ceramide**. Sphingomyelin degradation is catalyzed by acid and neutral **sphingomyelinase** (SMase) isoforms. Most, if not all mammalian cells, appear capable of signaling through the sphingomyelin pathway. Diverse receptor types and environmental stresses utilize the sphingomyelin pathway as a downstream effector system. In some cellular systems, **ceramide** initiates differentiation or cell proliferation, while in other systems, **ceramide** signals **apoptosis**. Recent investigations link the activation of neutral SMase to the extracellular signal regulated kinase (ERK) cascade and pro-inflammatory responses, and acid SMase to the stress-activated protein kinase/c-jun kinase (SAPK/JNK) cascade and apoptotic responses. Environmental stresses act directly on membrane to activate acid pH-dependent **sphingomyelinase** (ASMase), whereas cytokine receptors signal ASMase activation through motifs termed death domains.

The present review focuses on mechanisms of activation of ASMase and on ceramide signaling of the apoptotic response.

L20 ANSWER 16 OF 33 MEDLINE

96319722 Document Number: 96319722. PubMed ID: 8706124. Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis. Santana P; Pena L A; Haimovitz-Friedman A; Martin S; Green D; McLoughlin M; Cordon-Cardo C; Schuchman E H; Fuks Z; Kolesnick R. (Laboratory of Signal Transduction, Memorial Sloan-Kettering Cancer Center New York, New York 10021, USA.) CELL, (1996 Jul 26) 86 (2) 189-99. Journal code: CQ4; 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.

AB Stress is believed to activate sphingomyelinase to generate ceramide, which serves as a second messenger in initiating the apoptotic response. Conclusive evidence for this paradigm, however, is lacking. In the present study, we used a genetic approach to address this issue directly. We show that lymphoblasts from Niemann-Pick patients, which have an inherited deficiency of acid sphingomyelinase activity, fail to respond to ionizing radiation with ceramide generation and apoptosis. These abnormalities are reversible up on restoration of acid sphingomyelinase activity by retroviral transfer of human acid sphingomyelinase cDNA. Acid sphingomyelinase knockout mice also expressed defects in radiation-induced ceramide generation and apoptosis in vivo. Comparison with p53 knockout mice revealed that acid sphingomyelinase-mediated apoptosis and p53-mediated apoptosis are likely distinct and independent. These genetic models provide definitive evidence for the involvement of acid sphingomyelinase in one form of stress-induced apoptosis

L20 ANSWER 17 OF 33 MEDLINE

95400295 Document Number: 95400295. PubMed ID: 7670466. Acid sphingomyelinase deficient mice: a model of types A and B Niemann-Pick disease. Horinouchi K; Erlich S; Perl D P; Ferlinz K; Bisgaier C L; Sandhoff K; Desnick R J; Stewart C L; Schuchman E H. (Department of Human Genetics, Mount Sinai School of Medicine, New York, New York 10029, USA.) NATURE GENETICS, (1995 Jul) 10 (3) 288-93. Journal code: BRO; 9216904. ISSN: 1061-4036. Pub. country: United States. Language: English.

AB Types A and B Niemann-Pick disease (NPD) result from the deficient activity of acid sphingomyelinase (ASM). An animal model of NPD has been created by gene targeting. In affected animals, the disease followed a severe, neurodegenerative course and death occurred by eight months of age. Analysis of these animals showed their tissues had no detectable ASM activity, the blood cholesterol levels and sphingomyelin in the liver and brain were elevated, and atrophy of the cerebellum and marked deficiency of Purkinje cells was evident. Microscopic analysis revealed 'NPD cells' in reticuloendothelial organs and characteristic NPD lesions in the brain. Thus, the ASM deficient mice should be of great value for studying the pathogenesis and treatment of NPD, and for investigations into the role of ASM in signal transduction and apoptosis.

L20 ANSWER 18 OF 33 MEDLINE

95382894 Document Number: 95382894. PubMed ID: 7544586. The sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor, Fas, and ionizing radiation. Kolesnick R N; Haimovitz-Friedman A; Fuks Z. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) BIOCHEMISTRY AND CELL BIOLOGY, (1994 Nov-Dec) 72 (11-12) 471-4. Ref: 37. Journal code: ALR; 8606068. ISSN: 0829-8211. Pub. country: Canada. Language: English.

AB Recent evidence suggests that tumor necrosis factor alpha, Fas, and ionizing radiation employ the sphingomyelin pathway to trigger apoptosis. The sphingomyelin pathway is initiated by hydrolysis of

plasma membrane sphingomyelin to generate **ceramide** via a **sphingomyelinase**. **Ceramide** serves as a second messenger stimulating a cascade of kinases and transcription factors that activate a final common pathway of programmed cell death. The extent to which this signaling system is used in **apoptosis** induced by other toxic modalities is not known, but accumulating evidence suggests that it is a commonly employed pathway that could be exploited therapeutically.

L20 ANSWER 19 OF 33 MEDLINE

95081117 Document Number: 95081117. PubMed ID: 7989341. Attenuation of **ceramide**-induced **apoptosis** by diglyceride in human myeloid leukemia cells. Jarvis W D; Fornari F A Jr; Browning J L; Gewirtz D A; **Kolesnick R N**; Grant S. (Department of Medicine, Medical College of Virginia, Richmond 23298.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Dec 16) 269 (50) 31685-92. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Prior studies demonstrated that increased intracellular availability of **ceramide** induces apoptotic DNA degradation and cell death in the human leukemia cell lines HL-60 and U937 (Jarvis, W. D., Kolesnick, R. N., Fornari, F. A., Traylor, R. S., Gewirtz, D. A., and Grant, S. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 73-77). The present findings show that diglyceride opposes **ceramide**-related **apoptosis** in HL-60 and U937 cells. Acute (6-12-h) exposure to **sphingomyelinase** (100 milliunits/ml) or synthetic **ceramide** (10 microM) promoted apoptotic degradation of genomic DNA as indicated by (a) the appearance of both approximately 50-kilobase pair (kbp) DNA fragments and approximately 0.2-1.2-kbp DNA fragment ladders on agarose gels, (b) formation and release of small double-stranded DNA fragments, and (c) loss of integrity of bulk DNA. DNA damage was associated with reduced clonogenicity and expression of apoptotic morphology. In contrast, exposure to phospholipase C (0.001-100 milliunits/ml) or synthetic diglyceride (10 microM) failed to promote **apoptosis** and abolished the lethal actions of **ceramide** as defined by each of the indices outlined above. **Ceramide**-related **apoptosis** was also reduced by acute (6-h) exposure to tumor promoters such as phorbol dibutyrate and mezerein and the non-tumor-promoting agent bryostatin 1; conversely, chronic (24-h) pretreatment with these agents failed to modify **ceramide**-mediated cytotoxicity, but abolished the protective actions of diglyceride. These findings demonstrate that diglyceride and pharmacological protein kinase C activators reduce or abolish **ceramide**-mediated **apoptosis** in human leukemia cells and support the concept of a cytoprotective function for protein kinase C in the regulation of leukemic cell survival. In addition, the capacity of diglyceride to prevent very early genomic lesions (e.g. generation of 50-kbp DNA fragments) suggests that acute activation of protein kinase C arrests **apoptosis** at an initial stage.

L20 ANSWER 20 OF 33 MEDLINE

94321907 Document Number: 94321907. PubMed ID: 8046331. Ionizing radiation acts on cellular membranes to generate **ceramide** and initiate **apoptosis**. Haimovitz-Friedman A; Kan C C; Ehleiter D; Persaud R S; McLoughlin M; Fuks Z; **Kolesnick R N**. (Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York 10021.) JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Aug 1) 180 (2) 525-35. Journal code: I2V; 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Recent investigations provided evidence that the sphingomyelin signal transduction pathway mediates **apoptosis** for tumor necrosis factor alpha (TNF-alpha) in several hematopoietic and nonhematopoietic cells. In this pathway, TNF-receptor interaction initiates sphingomyelin hydrolysis to **ceramide** by a **sphingomyelinase**. **Ceramide** acts as a second messenger stimulating a **ceramide**-activated serine/threonine protein kinase. The present studies show that ionizing radiation, like TNF, induces rapid sphingomyelin hydrolysis to **ceramide** and **apoptosis** in bovine aortic endothelial

cells. Elevation of **ceramide** with exogenous **ceramide** analogues was sufficient for induction of **apoptosis**. Protein kinase C activation blocked both radiation-induced sphingomyelin hydrolysis and **apoptosis**, and **apoptosis** was restored by **ceramide** analogues added exogenously. Ionizing radiation acted directly on membrane preparations devoid of nuclei, stimulating sphingomyelin hydrolysis enzymatically through a neutral **sphingomyelinase**. These studies provide the first conclusive evidence that apoptotic signaling can be generated by interaction of ionizing radiation with cellular membranes and suggest an alternative to the hypothesis that direct DNA damage mediates radiation-induced cell kill.

L20 ANSWER 21 OF 33 MEDLINE

94105189 Document Number: 94105189. PubMed ID: 8278410. Induction of apoptotic DNA damage and cell death by activation of the sphingomyelin pathway. Jarvis W D; **Kolesnick R N**; Fornari F A; Traylor R S; Gewirtz D A; Grant S. (Department of Medicine, Medical College of Virginia, Richmond 23298-0230.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Jan 4) 91 (1) 73-7. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The potential involvement of **ceramide**-related signaling processes in the induction of **apoptosis** by tumor necrosis factor alpha was assessed by multiple biochemical strategies in the human leukemic cell lines HL-60 and U937 and the murine fibrosarcoma cell lines L929/LM and WEHI 164/13. Exposure of these cells to tumor necrosis factor alpha resulted in internucleosomal cleavage of genomic DNA, yielding ladder patterns of oligonucleosomal fragments characteristic of **apoptosis** when resolved by agarose gel electrophoresis; similar responses were observed after exposure to exogenous **sphingomyelinase** or synthetic **ceramides**. Quantitative spectrofluorophotometry demonstrated that these treatments promoted time- and concentration-dependent degradation of DNA, resulting in the formation of and eventual release of small DNA fragments (< or = 3.0 kb). Corresponding damage to bulk DNA was demonstrated by enhanced-fluorescence alkaline unwinding analysis. DNA fragmentation was not induced by phospholipase C or synthetic diglyceride; in fact, the effects of **sphingomyelinase** and **ceramide** were substantially reduced by coexposure to these agents, suggesting opposing roles for diglyceride- and **ceramide**-mediated signals in the regulation of **apoptosis**. Phospholipase A2 and arachidonic acid failed to promote DNA fragmentation, as did phospholipase D. Characterization of DNA strand breaks by alkaline and neutral elution analyses confirmed that **ceramide** action was restricted to breakage of mature, double-stranded DNA but not of nascent DNA. The induction of DNA damage was associated with appearance of apoptotic morphology and decreased clonogenicity. These results demonstrate that the **ceramide**-dependent signaling system selectively induces **apoptosis** and raise the possibility that **ceramide**-activated enzymes represent important components in a signaling cascade involved in the regulation of programmed cell death.

L20 ANSWER 22 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001071586 EMBASE Niemann-Pick Disease versus acid **sphingomyelinase** deficiency [1]. Lozano J.; Morales A.; Cremesti A.; Fuks Z.; Tilly J.L.; **Schuchman E.**; Gulbins E.; **Kolesnick R.** R. Kolesnick, Laboratory of Signal Transduction, Mem. Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021, United States. Cell Death and Differentiation 8/1 (100-102) 2001. Refs: 29. ISSN: 1350-9047. CODEN: CDDIEK. Pub. Country: United Kingdom. Language: English.

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L21 0 STAUPINE AND APOPTOSIS

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